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VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/163,089	09/29/98	MCKENZIE I	4102-1

022442
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HM12/0728

EXAMINER	
OGIHARA, N	
ART UNIT	**PAPER NUMBER**
1631	12

DATE MAILED: 07/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/163,089	MCKENZIE ET AL.	
	Examiner	Art Unit	
	Nancy Ogihara	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-69 is/are pending in the application.

4a) Of the above claim(s) 2, 22, 35, 46, 52-69 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1, 3-21, 23-34, 36-45, and 47-51 is/are rejected.

7)☒ Claim(s) 28-31,41,42 and 51 is/are objected to.

8)☒ Claims 1-69 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other:

DETAILED ACTION

Claims 1-69 are pending in the instant application. Applicant's election with traverse of Group I, claims 1-51, with a 1st election of species of oxidized mannose, a 2nd election of species of cells with a biological response modifier, and a 3rd election of species of MUC1 as the antigen, as stated in the paper filed 7/5/00 is acknowledged.

The traversal is on the ground(s) that examination of all claims can be made without serious burden if restriction is not required and that examination of Groups I and II would be sufficient to examine the claims of Group II. Applicant further argues that with regards to the species elections, the mannose species are closely related, that the species election with and without a biological response modifiers is improper because the species are essentially further embodiments of the claims, and that search of claim 1 is sufficient to examine all of the recited antigens in claim 12.

Applicant's arguments have been fully considered, but they are not persuasive for the following reasons: Groups I-III, as set forth in the restriction requirement, are independent and distinct, as Invention I is drawn to a composition comprising cells and an antigen, while Invention III is drawn to a therapeutic compound which does not comprise cells. Cells and therapeutic (i.e. chemical) compounds are in separate biological classifications, and while their searches may be overlapping, there is no reason to believe that the searches would be co-extensive. Furthermore, the composition of Invention I is separate and distinct since it can be used in a materially different process such as identifying mannose receptor ligands in *in vitro* assays. Furthermore still, each of the mannose species is obtained by differing method steps and reagents resulting in chemically different compounds with differing properties; inclusion of a biological response modifiers is not an embodiment encompassed by the claims not including biological response modifiers; and finally, the antigens recited in Claim 12 each have differing sequences with differing structure/function properties, activities, chemical characteristics, and derived from a multitude of different organisms. Therefore, because their status in the art is divergent, Groups I-III are separate and distinct for the reasons given above, and there would be a serious burden placed on the examiner from further searching and consideration if the restriction were not required.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2, 22, 35, 46, 52-69 are withdrawn from further consideration as being drawn to a non-elected invention.

Priority

This application is a continuation-in-part of application 08/833,807, filed 04/09/97, now patented (Patent No. 5,989,552), which is a continuation of application 08/340,711, filed 11/16/94, now abandoned. This application also claims priority to provisional application 60/060,594, filed 09/29/97.

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Claim Rejections - 35 USC § 112

Claim 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mannan conjugated to human mucin (MUC1) (i.e. an antigen), does not reasonably provide enablement for conjugates comprised of fragments of MUC1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims

Applicant is claiming a composition comprising a mannose receptor-bearing cells and a conjugate between an antigen and mannose. Applicant goes on to limit the antigens which may be used to specifically recited list which includes an amino acid subunit of said antigen comprising five or amino acids in length. Applicant has not taught the selection of appropriate fragments of repeated subunits from within the sequence of the mucin polypeptide. Applicant has not taught the characteristics of fragments with sufficient clarity as to allow a person of ordinary skill to identify them. As Applicant is claiming fragments of the repeated subunits and not the entire subunits or molecules themselves, the specification lacks sufficient teaching and guidance so as to identify which

portions of human mucin, as well as the other claimed antigens, that can be used in the instant invention as an immunoregulatory composition. Applicant does not teach what characteristics a fragment must possess in order to be useful in the instant invention. For example, which amino acid sequences are critical and sufficient to fold into a 3-dimensional structure so as to be immunoregulatory for the stimulation of an intended response? Are five amino acids from any of the recited antigens sufficient?

Absent any specific instruction as to the selection of fragments, it would be unpredictable for a person of ordinary skill in the art to identify useful fragments without undue experimentation. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with claims.

Claims 1, 3-21, 23-34, 36-45, and 47-51are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mannan conjugated to human mucin (i.e. an antigen), does not reasonably provide enablement for conjugates comprised of mannose, or oxidized forms thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant claims a composition comprising a mannose receptor-bearing cells and a conjugate between an antigen and mannose. Applicant discloses the carbohydrate polymer mannan conjugated to human mucin (MUC1) in the specific examples (see Example 1, page 44, line 5; subsequent example use oxidized mannan). Applicant does not teach the use of any other carbohydrates for the practice of the instant invention. Mannose is a monosaccharide containing a single sugar moiety, and it is acknowledged that mannan is a polymer comprised of mannose units, oxidized or otherwise. However, mannose does not include mannan, and it is not certain that the two terms are being used synonymously. Mannan is a polymer with differing structural properties than a single mannose, therefore, it is not certain what properties or effects the polymer possesses for use in the claimed immunoregulatory composition that are absent in a single mannose molecule.

Because of the above mentioned uncertainties, the making and/or using of a composition comprising mannose and human MUC1 would be unpredictable and require undue experimentation as

the disclosed examples are directed to mannan and not mannose. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with claims.

Claims 11, 12, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 12, and 25 are vague and indefinite in the recitation of the several abbreviations (for example, MUC1, GM-CSF, M-CSF). The full names of abbreviations should be completely spelled out upon their first appearance and not abbreviated.

Claim 12 is confusing in the recitation of the term "amino acid subunit" of an antigen. It is unclear as to what applicant means by the term as applicant has failed to provide adequate instruction in the specification for the identification of an amino acid subunit. The term implies a portion of a single amino acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-15, 17-21, 23-27, 32-34, 36-40, 43-45, 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rodwell *et al.* (U.S. Patent No. 5,047,227), in view of Edelsen *et al.* (U.S. Patent No. 5,820,872), and in further view of Kjeldsen *et al.* (U.S. Patent No. 5,229,289).

Kjeldsen *et al.* teach the administration of high molecular weight glycoproteins isolated from human lung squamous cell carcinoma cell lines where said glycoproteins comprise the Tn antigen (see Example 1, columns 18-19) which is a mucin glycoprotein (see column 2, lines 8-10) . The glycoproteins are a conjugate between an antigen and a carbohydrate polymer comprised of a high degree of glycosylation and disulfide bond formation between protein subunits (i.e. repeated subunits) (see column 7, lines 20-25). The glycoproteins are identified as human mucins by monoclonal antibodies and appear to be the human mucin MUC1. Kjeldsen *et al.* further teach of preparing Tn antigens (eg. human mucin glycoconjugates) for use as immunizing antigens (see Example 4, column 30, lines 48-50). Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 ISPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Rodwell *et al.* teach of immunoregulatory compositions comprised of peptides conjugated to high mannose (i.e. 4-9 mannose units, see column 4, lines 51-56) containing antibodies (see abstract). This conjugation is accomplished by oxidation of mannose to form aldehydes (see column 5, lines 18-37) and followed by reaction of the oxidized mannose with free amine groups on proteins (such as antigens). Rodwell *et al.* teach that oxidation of the carbohydrate significantly increases the number of sites for coupling compounds (see column 2, lines 57-59) (i.e. antigens) to afford an enhanced sensitivity for intended applications (see column 10, lines 7-10) ostensibly because of the higher local concentration conjugated compound.

The combined teachings of Rodwell *et al.* and Kjeldsen *et al.* do not teach of immunoregulatory compositions further comprised of mannose receptor-bearing cells treated with cytokines.

Edelson *et al.* teach of compositions comprising macrophage (i.e. mannose receptor-bearing cells—see Stahl *et al.*, Current Opinion in Immunology, vol. 10, pp. 50-55, 1998) to be used as cellular vaccines. Edelson *et al.* disclose that cells can be isolated from blood, bone marrow, and lymph node tissue or fluid (see column 8, lines 33-59). To enhance antigen presentation, cells are prepared by incubating with cytokines (i.e. biological response modifiers) which include GM-CSF, interleukins, interferons, and tumor necrosis factor (see column 10, lines 1-16) in addition to being contacted with tumor-derived antigens. The composition further includes a pharmaceutically acceptable carrier for administration (see column 6, lines 57-63). As cellular vaccines, the treated cells presenting antigen are recognized by specific T-cell receptors to mediate cellular immune responses (i.e. immunoregulatory) (see column 2, lines 14-19).

Given that 1) that Rodwell *et al.* have taught of conjugating polypeptides to oxidized high mannose, 2) that Kjeldsen *et al.* teach of human MUC1 glycoprotein conjugates for use in immunization, and 3) that Edelson *et al.* have taught of compositions comprising mannose receptor-bearing cells, antigen, and cytokines for use as cellular vaccines, it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to conjugate human MUC1 of Kjeldsen *et al.* with oxidized mannan of Rodwell *et al.* to be used as an antigen in a composition further comprising mannose receptor-cells and cytokines such as GM-CSF of Edelsen *et al.* to form an immunoregulatory composition for use as a cellular vaccine. One of ordinary skill in the art would have been motivated to combine the above mentioned components in view of the potential advantages of enhanced immunogenicity of an antigen in a cellular vaccine.

Claims 1, 3-21, 23-27, 32-34, 36-40, 43-45, 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor-Papadimitriou *et al.* (WO 90/05142) in view of Rodwell *et al.* (U.S. Patent No. 5,047,227),and in further view of Edelsen *et al.* (U.S. Patent No. 5,820,872).

Taylor-Papadimitriou *et al.* teach of peptides derived from human polymorphic epithelial mucin and their use in immunization (see abstract). These peptides may be reiterated more than once (see claim 1). Taylor-Papadimitriou *et al.* teach that these peptides may be produced in a variety of ways, one of which is as a fusion protein (see pages 24-25) and teach the conjugation of these peptides to one or more saccharide moieties (see page 2). The disclosed fusion proteins can be used for

therapeutic purposes including increasing a patient's immunity (i.e. immunoregulatory composition) (see page 25, first half).

Taylor-Papadimitriou *et al.* do not specifically teach the conjugation of their peptides to oxidized mannose (or mannan) or of a composition comprising mannose receptor-bearing cells stimulated with cytokines.

The teachings of Rodwell and Edelsen *et al.* are set forth above.

Given that 1) Taylor-Papadimitriou *et al.* teach of immunoregulatory compositions comprised of mucin fusion polypeptides for modulating immunity, 2) that Rodwell *et al.* have taught of conjugating polypeptides to oxidized high mannose because oxidized mannose increases the number of coupling sites, and 3) that Edelson *et al.* have taught of compositions comprising mannose receptor-bearing cells, antigen, and cytokines for use as cellular vaccines, it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to the fuse mucin polypeptides of Taylor-Papadimitriou *et al.* with oxidized high mannose of Rodwell *et al.* to be used as an antigen in a composition further comprising mannose receptor-cells and cytokines such as GM-CSF of Edelsen *et al.* to form an immunoregulatory composition for use as a cellular vaccine. One of ordinary skill in the art would have been motivated to combine the above mentioned components in view of the potential advantages of enhanced immunogenicity of an antigen in a cellular vaccine.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Ogihara whose telephone number is (703) 308-9363. The examiner can be reached Monday-Friday from 8:30-6:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Michael Woodward can be reached at (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1631 by facsimile transmission. Papers should be faxed to Group 1631 via the PTO Fax Center located in Crystal Park I. The faxing of such papers must conform with the notice published in the Official 1Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Nancy Ogihara
July 25, 2000

ARDIN H. MARSCHEL
PRIMARY EXAMINER